PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Marie Ana Ghetie
Jonathan W. Uhr
Ellen S. Vitetta.

Group Art Unit: 1642

Examiner: Hunt, J.

Serial No.: 09/112,041

Atty. Dkt. No.: UTSD:521/MBW

Filed: 07/08/98

For: COMPOSITIONS AND METHODS FOR HOMOCONJUGATES OF ANTIBODIES WHICH INDUCE GROWTH ARREST OR APOPTOSIS OF TUMOR CELLS

CERTIFICATE OF MAILING
37 C.F.R. §1.8

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June 20, 2001
Date

Mark B. Wilson

BRIEF ON APPEAL

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Exhibit F – Ghetie, *et al.* (1996)
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APPEAL BRIEF

BOX AF
Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellant hereby submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action dated October 12, 2000, and the Advisory Action dated March 30, 2001. A Notice of Appeal was mailed on February 12, 2001, and received by the PTO on February 15, 2001. Thus, this brief is due on July 15, 2001 by virtue of the enclosed Petition for Extension of Time payment of fees. The fees for filing this Appeal Brief are attached hereto. Should any other fees be due, or the attached fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/10004051/01973. Please date stamp and return the enclosed postcard to evidence receipt of this document.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicant petitions for an extension of time of three months to and including 15 July 2001 in which to respond to the Notice of Appeal dated February 12, 2001, and received by the PTO on February 15, 2001. Pursuant to 37 C.F.R. § 1.17, a check in the amount of $600.00 is enclosed, which includes the small entity process fee for a three month extension of time ($445.00). If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Assistant Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/10017628/MW01999.

I. REAL PARTIES IN INTEREST

The real parties in interest are the assignee, The Board of Regents, University of Texas System, 201 West 7th Street, Austin, TX 78701.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interference.

III. STATUS OF THE CLAIMS

Claims 1-52 were filed in the original application. Claims 30-42 were canceled without prejudice or disclaimer in response to a restriction requirement of September 20, 1999. Claims 10, 24, and 52 were canceled without prejudice or disclaimer in reply to the Office Action of February 14, 2000.

A First Amendment under 37 C.F.R. § 1.116 was submitted after the Final Office Action of 12 October 2000. In the Advisory Action, the Examiner indicated that this First Amendment will be entered upon filing of this Appeal Brief. Upon entry of the First Amendment, claims 2, 3, 6, 12-15, 18-20, 26-42, 44, 45, and 48 will have been canceled without prejudice or disclaimer. Thus, claims 1, 4, 5, 7-9, 11, 16, 17, 21-23, 25, 43, 46, 47, and 49-51 are pending in the case and stand appealed.

Appellants point out that the Advisory Action also removed all present rejections of the subject matter of claims 4, 5, 16, 17, 46 and 47. Therefore, in order to expedite the resolution of this case, Appellants have submitted a Second Amendment under 37 C.F.R. § 1.116, concurrent with this Appeal Brief, placing the subject matter of these claims into the independent claims of this case. All other claims remaining in the case depend from these claims, and after amendment, claims 4, 5, 16, 17, 46 and 47 will be cancelled. Entry of the Second Amendment thus eliminates ***all*** issues on appeal and presents the claims in the best possible form for consideration. Appellants submit that the Second Amendment on its face clearly places the application in condition for allowance and therefore should be entered. MPEP § 1207, paragraph 2.

A summary of the claims as they exist after entry of both the First and Second Amendments is presented in Appendix 1. A summary of the claims as they would exist after entry of only the First Amendment is presented in Appendix 2.

IV. STATUS OF AMENDMENTS

Two amendments have been filed after the Final Office Action: the First Amendment in response to the Final Office Action, the Second Amendment concurrent with this Appeal Brief.

In the Advisory Action, the Examiner indicated that the First Amendment will be entered upon filing of this Appeal Brief.

The Second Amendment is submitted herewith. The Second Amendment places the allowable subject matter of claims 4, 5, 16, 17, 46 and 47 into the independent claims of the case. Entry of the Second Amendment will not necessitate any new searches, presents no new matter, reduces the number of claims in the case, and introduces no new issues. In fact, entry of the Second Amendment will moot the Appeal.

Submission of this amendment was, of course, impossible prior to the issuance of the Advisory Action since the allowable subject matter was only first identified in that Action. Although Appellants recognize that no amendment may be made as a matter of right in appealed cases, 37 C.F.R. §1.116(d), Appellants respectfully submit that no impediment to entry of the Second Amendment exists under 37 C.F.R. § 1.116(b) or (c). Moreover, since entry will result in the resolution of the case by removing all pending rejections, entry is proper. Appellants submit that the Second Amendment on its face clearly places the application in condition for allowance and therefore should be entered. MPEP § 1207, paragraph 2. Entry of the Second Amendment is respectfully requested.

A summary of the claims as they exist after entry of both the First and Second Amendments is presented in Appendix 1. A summary of the claims as they exist after entry of only the First Amendment is presented in Appendix 2. Copies of both Amendments are attached as Exhibits A and B in Appendix 3.

V. SUMMARY OF THE INVENTION

The present invention is drawn to monoclonal antibodies that have little or no signaling activity as monomers, but which become potent anti-tumor agents when converted into

homoconjugates. The homoconjugates exert anti-growth activity by signaling G0/G1 arrest or apoptosis, depending upon the cell surface molecule they bind. This activity is specific and does not require an Fc portion. These conjugates are potent antitumor agents. The invention includes methods of making and using such homoconjugates and pharmaceutical compositions comprising the homoconjugates.

VI. ISSUES ON APPEAL

A. There are no issues on appeal if the Second Amendment is entered.

The Advisory Action withdrew rejections of claims 4, 5, 16, 17, 46, and 47 under 35 U.S.C. § 102(b) as anticipated by Ahlem *et al.*, U.S. Patent 5,273,743. See Advisory Action page 2, paragraph 1. Despite the assertion of the Advisory Action that "No claims are allowed," (Advisory Action page 5, line 11), and the assertion on the cover sheet that these claims are rejected for purposes of appeal, no further grounds of rejection are of record against these claims.

There is no other rejection of claims covering this subject matter but those based on the prior art. Those rejections having been withdrawn with respect to the subject matter of these claims, they stand allowable upon entry of both amendments under 37 C.F.R. § 1.116. Because all of the remaining rejected claims depend from these amended claims, their rejections should be moot upon entry of the amendment. Therefore, entry of the Second Amendment under 37 C.F.R. § 1.116 will remove ***all*** issues on appeal and result in an expedited resolution of this case. For reasons presented above (see **III** and **IV**) there is no bar to the entry of the second amendment and quick resolution of this case.

If the Second Amendment is not entered, the following issues are on appeal.

B. Whether claims 1, 3, 9, 11, 13, and 23 are anticipated by Bagshawe.

C. Whether claims 1-3, 6-15, 18-25, 43-45 and 48-51 are obvious under 35 U.S.C. § 103(a) over the Glennie, Ghetie, and Bosslet in view of Wolff.

VII. GROUPING OF THE CLAIMS

Whether the claims stand or fall together depends upon whether both amendments are entered. If both the First and Second Amendments are entered, there is no remaining ground for rejection of any claim and the claims stand together and allowable.

If only the First Amendment is entered, the claims do not stand or fall together because the claims rejected under 35 U.S.C. § 102(e) are a subset of the claims rejected under 35 U.S.C. § 103(a). Specifically, if the grounds for rejection under 35 U.S.C. § 102(e) are upheld, but the grounds for rejection under 35 U.S.C. § 103(a) are overturned, then claims 2, 6-8, 10, 12-15, 18, 19-22, 24, 25, 43-45, and 48-51 stand allowable. Conversely, if the rejection under 35 U.S.C. § 103(a) is upheld all the claims fall together.

VIII. ARGUMENT

A. Upon entry of the Second Amendment, there will be *no* issues on appeal, and the claims will stand allowable.

The Advisory Action withdrew rejections of claims 4, 5, 16, 17, 46, and 47 under 35 U.S.C. § 102(b) as anticipated by Ahlem *et al.*, U.S. Patent 5,273,743. See Advisory Action page 2, paragraph 1. Despite the assertion of the Advisory Action that "No claims are allowed," (Advisory Action page 5, line 11), and the assertion on the cover sheet that these claims are rejected for purposes of appeal, no further grounds of rejection are of record against these claims.

There is no other rejection of claims covering this subject matter but those based on the prior art. Those rejections having been withdrawn with respect to the subject matter of these

claims, they stand allowable upon entry of the Second Amendment under 37 C.F.R. § 1.116. Because all of the remaining rejected claims depend from these amended claims, these rejections are mooted.

If entry of the Second Amendment is denied, the following argument overcomes the rejections remaining after entry of the First Amendment.

B. Because Bagshawe does not disclose all aspects of the invention, Bagshawe does not anticipate claims 1, 3, 9, 11, 13, and 23.

The Final Office Action alleges that claims 1, 3, 9, 11, 13 and 23 are anticipated by Bagshawe *et al.*, U.S. Patent No. 5,683,694 (1997), (hereafter Bagshawe) under 35 U.S.C. § 102(e). Appellants traverse the rejection for the reasons set forth in previous responses.

The Final Action contends that Bagshawe *et al.* teach a conjugate comprising a monoclonal antibody that does not comprise an Fc region and exhibits anti-neoplastic activity. The Action also states that Bagshawe teaches how to make such a conjugate using a mammalian monoclonal antibody. But, as described at Column 1, lines 14-20 of Bagshawe, this reference concerns antibody fragments capable of binding a tumor-associated antigen and which are bound to an enzyme capable of converting a prodrug into a cytotoxic drug. At column 2, lines 24-40, Bagshawe discusses a "first component" which is a "conjugate of an antibody to a tumor associated antigen or a fragment thereof that includes the antigen binding site of the antibody, wherein the antibody or fragment thereof is conjugated directly, or indirectly through a linking component, to an enzyme or to an antibody or fragment with catalytic functions."

The arguments submitted after the Final Action make clear the distinction between the art disclosed in Bagshawe *et al.* and the present invention. Nevertheless, in the Advisory Action,

the examiner continues to assert that "[a]nything which is part of the conjugate could exert anti-neoplastic activity and still anticipate the claim." See Advisory Action page 3, lines 8-9.

This is in contrast to the claimed invention, which contains the limitation that the conjugate exhibits anti-neoplastic activity and that the components prior to conjugation display no such activity. The use of an antibody as a targeting molecule for a cytotoxic agent does not anticipate this limitation, as it is the cytotoxic agent that exhibits the anti-neoplastic activity, not the homoconjugates *per se*. The inventors have found that homoconjugates of component antibodies lacking any anti-neoplastic activity are capable of causing target cells to undergo cell cycle arrest and/or apoptosis initiated by negative signaling resulting from the binding and hypercrosslinking of cell surface antigens to the homoconjugate. The creation of this anti-neoplastic activity is from components lacking such activity. Because Bagshawe lacks at least this aspect of the claimed invention, the claims are not anticipated.

In view of the foregoing, Applicants respectfully request that the Board overturn the rejection of claims 1, 3, 9, 11, 13 and 23 under 35 U.S.C. § 102(e).

C. Because the cited references may not be properly combined, claims 1-3, 6-15, 18-25, 43-45, and 48-51 are not obvious under 35 U.S.C. §103(a) over Glennie, Ghetie, or Bosslet in view of Wolff.

The Advisory Action has maintained the rejection of claims 1-3, 6-15, 18-25, 43-45 and 48-51 under 35 U.S.C. § 103(a) as being unpatentable over Glennie, WO 91/03493, 21 March 1991, (Glennie), Ghetie *et al.*, Exp. Opin. Invest. Drugs, Vol 5, No 3, pages 309-321, 1996, (Ghetie), or Bosslet *et al.*, US Patent 5,591,828, 7 January 1997 (Bosslet) in View of Wolff *et al.*, WO 92/04053 (Wolff).

The Actions allege that the cited references teach antibody homoconjugates exhibiting anti-neoplastic activity. Applicants again traverse.

1. The cited references teach away from the claimed invention.

As set forth in the prior Response to the Final Office Action, the cited references do not teach or suggest the claimed homoconjugates having anti-neoplastic activity. The references disclose conjugate antibodies comprised of component fragments with specificities that differ among them. Homoconjugates, as claimed in the instant application, are comprised of component fragments possessing substantially equivalent specificities. The Glennie, Ghettie, and Bosslet references do not teach, disclose, or mention homocongjuates. Instead, they teach the benefits and utilities of heteroconjugates of components with differing specificities.

First, Glennie relies on differences in specificity of the component fragments (bispecificity) to bring about its desired effect on the target cell. As is described at page 1, lines 13-30 of Ghettie , bispecific antibodies are used in which one specificity is directed to a target cell and another specificity is directed to the desired effector molecule, such as a toxic agent or effector T-cells. Various of such constructs, each having two or three specificities, are described at pages 10-11. Therefore, one of ordinary skill in the art would be taught by Glennie that

bispecificity is neccesary to achieve the goals of Glennie. As such, Glennie specifically teaches away from use of homoconjugates and cannot properly be combined with other references concerning the use of homoconjugates.

Similarly, as was described in the ealier Response, all of the conjugates in Ghetie are heteroconjugates. The reference also fails to suggest homoconjugates. Therefore, again, this reference cannot be properly combined with references allegedly suggesting use of homoconjugates. It is further noted that the anti-neoplastic activity allegedly exhibited by the cited heteroconjugates in Ghetie is not caused by the conjugates but by linked cytotoxic moieties.

Bosslet also teaches away from the use of a homoconjugate. In particular, the reference relies on a heteroconjugate comprising "F(ab) fragments of antibodies of two or more different specificities by means of suitable linkers." See Col. 1, lines 10-15. Once again, two specificities are used to achieve the desired results. See Col. 1, lines 66-67 and Col. 2 lines 1-3. Thus, this reference also teaches away from the claimed homoconjugates.

2. *The Wolff reference may not be combined with the other cited references.*

The "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Here, not only is there no suggestion to combine, but the aforementioned references ***teach away*** from a combination or modification in view of Wolff.

According to the Examiner, the Wolff reference "teaches antibody conjugates which are homoconjugates including dimers and multimers and that said conjugates are desirable because

the [sic] produce an enhanced immune response." Advisory Action at page 8, lines 3-5. But this teaching could ***not*** lead one skilled in the art towards the present invention. Here, the aforementioned references teach away from a combination with Wolff or other references concerning homoconjugates because Glennie, Ghetie, and Bosslet teach heteroconjugates. Glennie, Ghetie, and Bosslet are at best silent as to homoconjugates or homodimers. (See Advisory Action page 8, lines 1-2.)

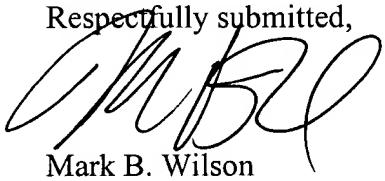
Contrary to the Examiner's assertion, (see Advisory Action page 4, lines 11-13), the suggestion that homoconjugates would be desirable cannot be read into the references' silence regarding homoconjugates. Rather, the combination or modification of any one of Glennie, Ghetie, or Bosslet with the disclosure of homocongjugates in Wolff would be expected to produce a seemingly inoperative conjugate within the context of Glennie, Ghetie, and Bosslet because the conjugate would not possess bispecific activities. Because Glennie, Ghetie, and Bosslet references teach away from the present invention Wolff cannot be properly combined with them to assert a *prima facie* case of obviousness. See *In re Sponnoble*, 160 USPQ 237, 244 (CCPA 1969).

In view of the foregoing, Appellants respectfully request that the Board overturn the rejection of claims 1-3, 6-15, 18-25, 43-45, and 48-51 under 35 U.S.C. § 103(a).

IX. CONCLUSION

It is respectfully submitted, in light of the foregoing, that all pending claims are novel under 35 U.S.C. 102(e) and entitled to their statutory presumption of non-obviousness under 35 U.S.C. 103(a). Appellants request that the Board allow all claims as they stand after entry of both the First and Second Amendments under 37 C.F.R. §1.116 or overturn the pending grounds for rejection after entry of only the First Amendment and allow all claims.

Respectfully submitted,



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Date: June 20, 2001

APPENDIX 1

STATE OF THE CLAIMS AFTER ENTRY OF BOTH FIRST AND SECOND AMENDMENTS

1. A homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, wherein the homoconjugate comprises an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody, wherein the homoconjugate has anti-neoplastic activity and wherein said monoclonal antibody has substantially no anti-neoplastic activity in an unconjugated form.

2. [Cancelled]

3. [Cancelled]

4. [Cancelled]

5. [Cancelled]

6. [Cancelled]

7. The homoconjugate of claim 1, further defined as a homodimer.

8. The homoconjugate of claim 1, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

9. The homoconjugate of claim 8, wherein the IgG is a mammalian IgG.

10. [Cancelled]

11. A method of making a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region and wherein the monoclonal antibody is an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody, comprising:

obtaining a first monoclonal antibody that does not comprise an Fc region;

obtaining a second monoclonal antibody that does not comprise an Fc region; and

conjugating the first monoclonal antibody to the second monoclonal antibody, wherein the first and second monoclonal antibodies have anti-neoplastic activity in a conjugated form and have substantially no anti-neoplastic activity in an unconjugated form.

12. [Cancelled]

13. [Cancelled]

14. [Cancelled]

15. [Cancelled]

16. [Cancelled]

17. [Cancelled]

18. [Cancelled]

19. [Cancelled]

20. [Cancelled]

21. The method of claim 11, wherein the homoconjugate is further defined as a homodimer.

22. The method of claim 11, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

23. The method of claim 11, wherein the homoconjugate comprises a mammalian monoclonal antibody.

24. [Cancelled]

25. The method of claim 11, further consisting of:
obtaining a third monoclonal antibody; and
conjugating the third monoclonal antibody to the homoconjugate.

26-42. [Cancelled]

43. A pharmaceutical composition comprising a homoconjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier, wherein the monoclonal antibody does not comprise an Fc region and wherein the monoclonal antibody is an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody and wherein the monoclonal antibody has anti-neoplastic activity in a conjugated form and has substantially no anti-neoplastic activity in an unconjugated form.

44. [Cancelled]

45. [Cancelled]

46. [Cancelled]

47. [Cancelled]

48. [Cancelled]

49. The pharmaceutical composition of claim 43, wherein the homoconjugate is further defined as a homodimer.

50. The pharmaceutical composition of claim 43, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

51. The pharmaceutical composition of claim 43, wherein the homoconjugate comprises a mammalian monoclonal antibody.

52. [Cancelled]

APPENDIX 2

STATE OF THE CLAIMS AFTER ENTRY OF ONLY THE FIRST AMENDMENT

1. A homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, wherein the homoconjugate has anti-neoplastic activity and wherein said monoclonal antibody has substantially no anti-neoplastic activity in an unconjugated form.

2. [Cancelled]

3. [Cancelled]

4. The homoconjugate of claim 3, wherein the homoconjugate comprises an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody.

5. The homoconjugate of claim 3, wherein the homoconjugate comprises an anti-Her2 monoclonal antibody.

6. [Cancelled]

7. The homoconjugate of claim 1, further defined as a homodimer.

8. The homoconjugate of claim 1, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

9. The homoconjugate of claim 8, wherein the IgG is a mammalian IgG.

10. [Cancelled]

11. A method of making a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, comprising:

obtaining a first monoclonal antibody that does not comprise an Fc region;

obtaining a second monoclonal antibody that does not comprise an Fc region; and

conjugating the first monoclonal antibody to the second monoclonal antibody, wherein the first and second monoclonal antibodies have anti-neoplastic activity in a conjugated form and have substantially no anti-neoplastic activity in an unconjugated form.

12. [Cancelled]

13. [Cancelled]

14. [Cancelled]

15. [Cancelled]

16. The method of claim 14, wherein the monoclonal antibody is an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody.

17. The method of claim 14, wherein the monoclonal antibody is an anti-Her2 monoclonal antibody.

18. [Cancelled]

19. [Cancelled]

20. [Cancelled]

21. The method of claim 11, wherein the homoconjugate is further defined as a homodimer.

22. The method of claim 11, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

23. The method of claim 11, wherein the homoconjugate comprises a mammalian monoclonal antibody.

24. [Cancelled]

25. The method of claim 11, further consisting of:
obtaining a third monoclonal antibody; and
conjugating the third monoclonal antibody to the homoconjugate.

26-42. [Cancelled]

43. A pharmaceutical composition comprising a homoconjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier, wherein the monoclonal antibody does not comprise an Fc region and wherein the monoclonal antibody has anti-neoplastic activity in a conjugated form and has substantially no anti-neoplastic activity in an unconjugated form.

44. [Cancelled]

45. [Cancelled]

46. The pharmaceutical composition of claim 43, wherein the monoclonal antibody is an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody.

47. The pharmaceutical composition of claim 43, wherein the monoclonal antibody is an anti-αHer2 monoclonal antibody.

48. [Cancelled]

49. The pharmaceutical composition of claim 43, wherein the homoconjugate is further defined as a homodimer.

50. The pharmaceutical composition of claim 43, wherein the homoconjugate comprises a monoclonal antibody that is an IgG monomer.

51. The pharmaceutical composition of claim 43, wherein the homoconjugate comprises a mammalian monoclonal antibody.

52. [Cancelled]

APPENDIX 3 – EXHIBITS

Exhibit A – First Amendment under 37 C.F.R. § 1.116

Exhibit B – Second Amendment under 37 C.F.R. § 1.116

Exhibit C – Bagshawe, *et al.*, U.S. Patent 5,683,694 (1997)

Exhibit D – Glennie, Patent WO 91/03493 (1991)

Exhibit E – Bosslet, *et al.*, US Patent 5,591,828 (1997)

Exhibit F – Ghetie, *et al.* (1996)

Exhibit G – Wolff, *et al.* Patent WO 92/04053 (1992)